European Journal of Clinical and Experimental Medicine

ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

**Authors**: Kumbha Nagalakshmi, Nair Parvati Ramachandran, Swetha Lakshmi Narla, Annapurneswari Subramanyan, Brundha Marimuthu Parasuraman

**Article type**: Case Report

**Received**: 31 January 2024

**Accepted**: 7 April 2024

**Published online**: 14 May 2024

**eISSN**: 2544-1361

**Eur J Clin Exp Med**

**doi**: 10.15584/ejcem.2024.3.11

ONLINE FIRST Eur J Clin Exp Med

**This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting and typesetting. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.**

This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY 4.0) license.

# Atypical presentation of extra-skeletal Ewing's sarcoma in a 57-year-old female – a case report

Kumbha Nagalakshmi [1], Nair Parvati Ramachandran [2], Swetha Lakshmi Narla [3], Annapurneswari Subramanyan [4], Brundha Marimuthu Parasuraman [4]

[1] Pathology and Medical Superintendent, Bharat Heavy Electricals Limited, Power Sector Southern Region, Chennai, Tamilnadu, India

[2] Department of Pathology, GEM Hospital, Chennai, Tamilnadu, India

[3] Department of Pathology, Apollo Hospitals, Chennai, Tamilnadu, India

[4] Department of Pathology, Madha Medical College and Research Institute, Chennai, Tamilnadu, India

**Corresponding author**: Brundha Marimuthu Parasuraman, e-mail: mpbrundha7@gmail.com

**ORCID**

MPB: https://orcid.org/0000-0002-3040-0780

Exp Med

## ABSTRACT

**Introduction and aim**. Malignant soft tissue tumors exhibiting similar histological and immunohistochemical characteristics to Ewing sarcoma of the bones are referred to as extra-skeletal Ewing sarcoma within the pathology research domain. These tumors fall under the broader classification of Ewing sarcoma family of tumors, which encompasses Ewing sarcoma of the bones, extra-skeletal Ewing sarcoma, and primitive neuroectodermal tumor, the latter demonstrating a more pronounced neural differentiation compared to Ewing sarcoma of the bone. Extra-skeletal Ewing sarcoma stands out as a rare, aggressive, and rapidly growing malignant soft tissue tumor characterized by a notable recurrence rate and a predilection for occurrence in males. The roots of recognizing extra-skeletal Ewing sarcoma trace back to 1975 when Angervall and Enzinger reported the inaugural case. This study aims to underscore the significance of recognizing diverse clinical presentations for precise diagnosis and effective patient care of Extra-skeletal Ewing sarcoma in an elderly patient.

**Case description**. In the context of our pathology research, a noteworthy case involves a 57-year-old female presenting with a mass in the left iliac fossa. The diagnosis, established through a comprehensive approach involving Imaging, histopathological examination, immunohistochemistry, and molecular studies such as fluorescence in situ hybridization, confirms the nature of the tumor as extra-skeletal Ewing sarcoma. This case adds to the understanding and documentation of this distinct variant through a multi-modal investigative process.

**Conclusion.** This case report contributes to the existing literature by shedding light on an atypical presentation of extra-skeletal Ewing sarcoma in an older patient. Understanding the varied clinical manifestations and incorporating advanced diagnostic techniques, such as fluorescence in situ hybridization and immunohistochemistry, is pivotal for accurate diagnosis and optimal patient management.
**Keywords**. Ewing sarcoma, Ewing sarcoma family of tumors primitive neuroectodermal tumor, extra skeletal Ewing sarcoma

## Introduction

Ewing Sarcoma stands as a highly malignant bone tumor primarily affecting long bones, a condition notably prevalent in children and young adults. The pioneering description of this pathology traces back to James Ewing in 1921.[1] Despite its primarily osseous manifestation, instances of malignant soft tissue tumors exhibiting indistinguishable features from Ewing sarcoma have been documented, termed as extra-skeletal Ewing's Sarcoma. These tumors are presently categorized under the Ewing sarcoma family of tumors, encompassing Ewing sarcoma, extra-skeletal Ewing sarcoma, and the primitive neuroectodermal tumor, the latter demonstrating heightened neural differentiation compared to Ewing sarcoma.[2]

Extra-skeletal Ewing sarcoma, characterized by rarity and aggressiveness, represents a malignant soft tissue tumor with a notable recurrence rate, predominantly affecting adolescents and young adults within the age range of 10 to 30 years. The initial recognition of extra-skeletal Ewing sarcoma dates back to 1975 when Angervall and Enzinger reported the inaugural case.[3] Common sites of occurrence include the chest wall, paravertebral region, retroperitoneal space, lower extremities, and gluteal region. Uncommonly, cases have been reported in various locations such as the kidney, breast, gastrointestinal tract, prostate, endometrium, adrenal glands, brain, and lungs.[4]

Extra-skeletal Ewing sarcoma remains a challenging entity within the realm of medical literature, often posing diagnostic and therapeutic dilemmas. Diagnostic endeavors primarily rely on magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging techniques, allowing for initial diagnosis and the detection of potential metastases.[5] Extra-skeletal Ewing sarcoma emerges as a swiftly progressing tumor, primarily afflicting the young demographic, often posing a poor prognosis with notably high mortality rates, especially in cases of metastasis to the lungs, bones, and bone marrow. This pathology develops within the soft tissues of diverse anatomical regions, with the upper thigh, upper arms, shoulders, and buttocks being common sites.[6] The lack of specific clinical signs often contributes to delayed diagnosis, underscoring the importance of imaging in diagnosis, staging, preoperative assessment, and surveillance. Early diagnosis is imperative for effective management and intervention in this challenging medical condition.[7]

**Aim**

This study aims to underscore the significance of recognizing diverse clinical presentations for precise diagnosis and effective patient care of extra-skeletal Ewing sarcoma in an elderly patient.

**Description of the case**

A 57-year-old female sought evaluation in the Outpatient Department due to severe abdominal pain. Upon examination, a palpable mass was identified in the left iliac fossa. Ultrasonography revealed a substantial solid cystic intraperitoneal mass measuring 12.9×12.3×8.7 cm. The mass exhibited invasion of the left rectus muscle anteriorly and close proximity to small bowel loops posteriorly. Potential differentials were considered, with neoplasm (likely small bowel Gastro Intestinal Stromal Tumor) being the primary consideration, and hematoma deemed less likely. Biopsy was recommended for further confirmation.

Magnetic Resonance Imaging of the abdomen unveiled a large, heterogeneous, relatively defined solid cystic mass originating from the peritoneal surface of the left rectus muscle. Its superior extension reached from the level of the umbilicus, while its inferior extension reached into the left iliac fossa. Notably, no omental thickening or deposits were observed, with mild fluid present in the pelvis. Positron emission tomography–computed tomography imaging findings suggested a soft tissue or small bowel gastro intestinal stromal tumor.

Histopathological examination revealed features consistent with an abdominal wall malignant round cell neoplasm. Immunohistochemistry further indicated characteristics aligning with the Ewing sarcoma family of tumors. This comprehensive diagnostic approach underscores the complexity of the pathology and guides further management decisions.

***Gross examination***

Upon receipt, the mass exhibited adherence to fat and an attached ellipse of skin. A tag was identified, and the specimen was appropriately oriented. The mass with attached fibro-fatty tissue, measured 12×10×9 cm, while the attached skin measured 3.5×1 cm (Fig. 1).

ONLINE FIRST

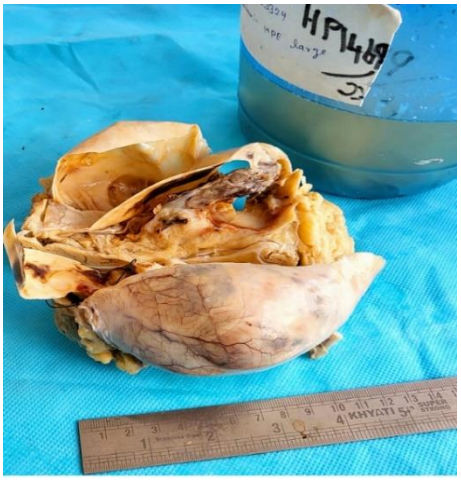

**Fig. 1**. Gross examination: Solid to cystic mass with areas of necrosis

Upon cutting, as shown in the Figure 1, the cut surface showed a tumor which displayed a combination of solid and cystic areas, cysts extruded hemorrhagic serous fluid. The largest solid area within tumor, measuring 9×4×6 cm, exhibited a variegated appearance with necrosis and hemorrhagic areas. Notably, the tumor displayed adjacency to the right lateral margin. This detailed gross examination provides a comprehensive overview of the specimen's macroscopic features, informing further pathological analysis and interpretation.

***Microscopic examination***

Upon microscopic examination, sections of the anterior abdominal mass revealed sheets of malignant-looking small round cells characterized by hyperchromatic nuclei, indistinct nucleoli, occasional mitosis, and scant to moderate eosinophilic cytoplasm (Fig. 2).

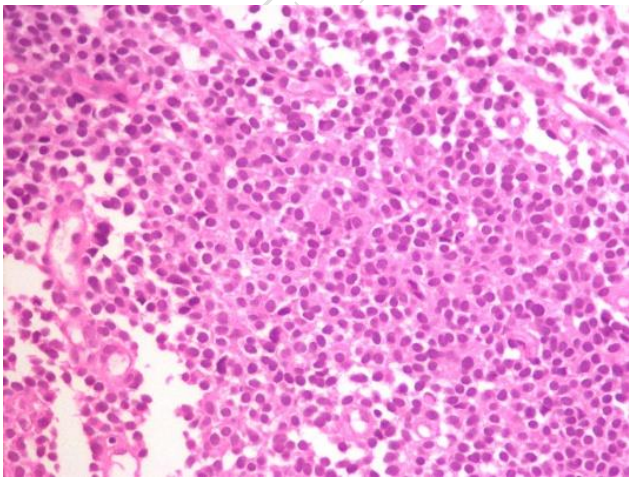

**Fig. 2**. Histopathology under high power view showed malignant small round cells (Hemotoxyllin &Eosin, 40×)

FIRST Eur J Clin Exp Med

Figures 2 shows the microscopic examination in high-power view providing detailed visualizations of the cellular composition and structural characteristics. Initial impressions were that the features observed in the anterior abdominal mass are indicative of a malignant small round cell tumor. To confirm and subtype the tumor, immunohistochemistry (IHC) is recommended. The comprehensive immunohistochemistry (IHC) panel was conducted on the anterior abdominal wall mass, yielding the following results: cytokeratin (CK): negative; vimentin: diffuse positive; leukocyte common antigen (LCA): negative; synaptophysin: weak positive; proliferation index marker – Ki-67: 10–15%; desmin: negative; muscle markers-MYOD1: negative; CD99: positive (membranous); FLI-1: positive; B-COR: negative; NKX2.2: positive. The respective Figures 3–8 illustrate the immunohistochemistry results, visually highlighting the expression of specific markers.

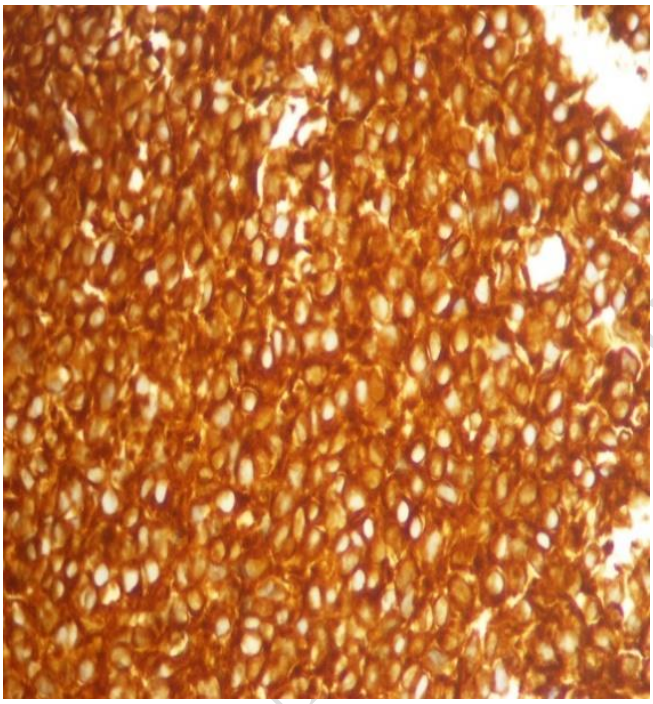

**Fig. 3**. Vimentin IHC staining showed diffuse cytoplasmic positivity

ONLINE ... ur J Clin Exp Med

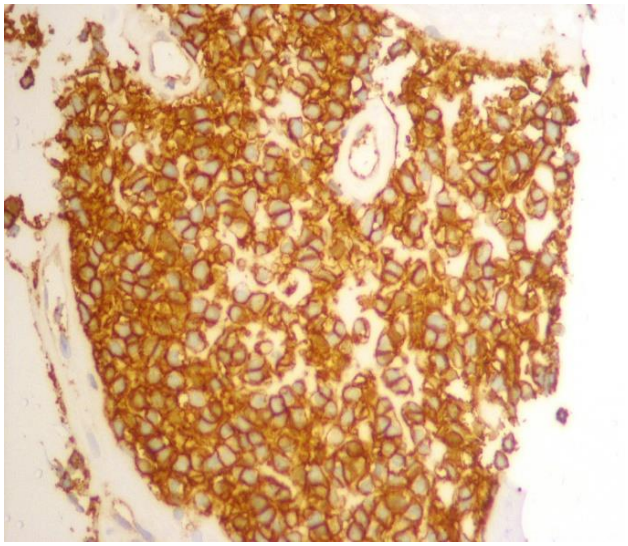

**Fig. 4**. CD-99 IHC staining showed strong membranous positivity

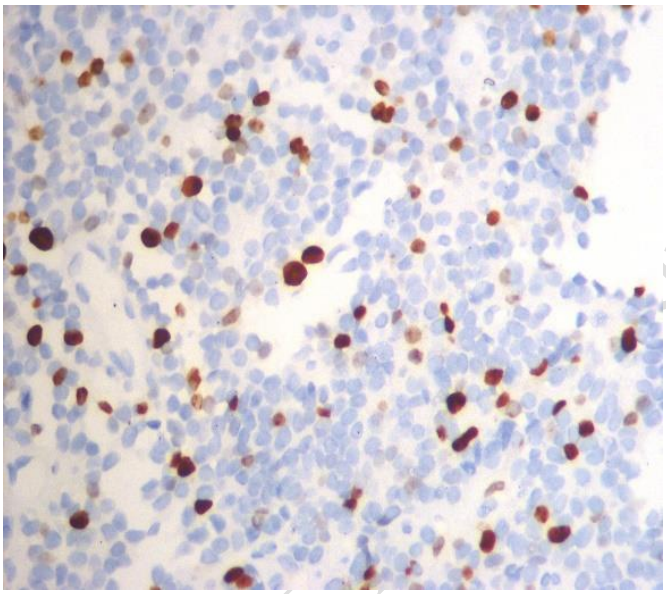

**Fig. 5**. Ki-67 IHC staining showed 10–15% nuclear positivity

ONLINE ... ur J Clin Exp Med

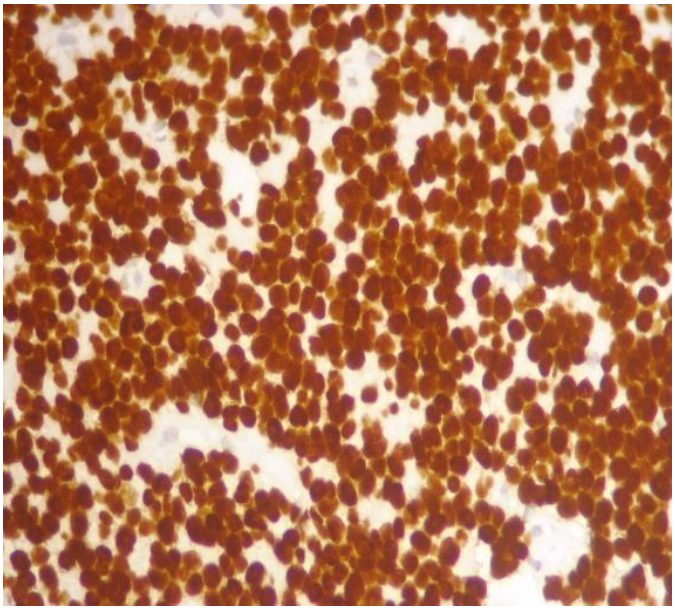

**Fig. 6**. NKX 2.2 IHC staining showed strong positivity

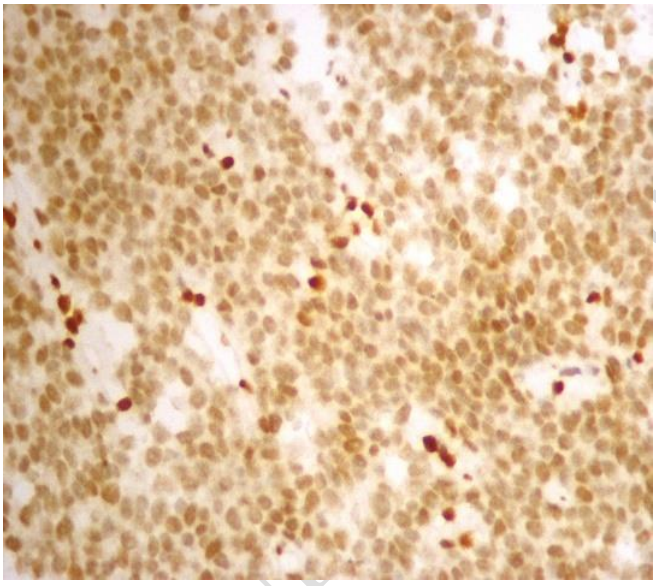

**Fig. 7**. FLI-1 IHC staining showed strong positivity

ONLINE First Our J Clin Exp Med

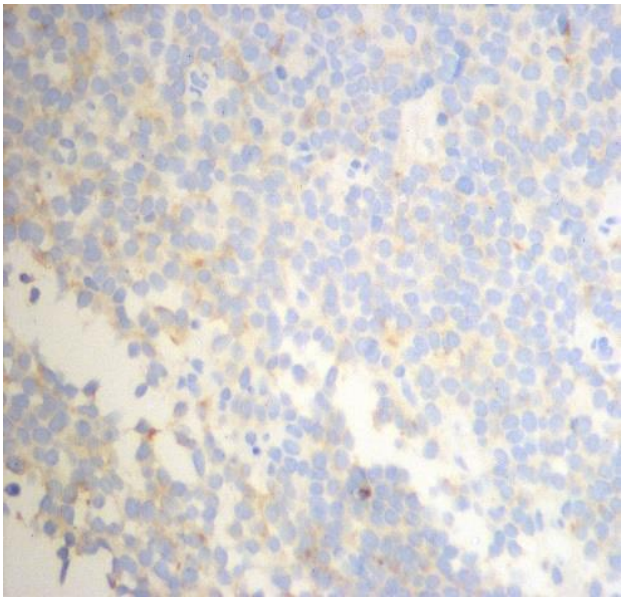

**Fig. 8.** Synaptophysin IHC staining showed weak positivity

Further genetic analysis using fluorescence in situ hybridization (fluorescence in situ hybridization ) of tumor nuclei in a representative section (Fig. 9) revealed positivity for Ewing sarcoma breakpoint region-1(EWSR1) in chromosome 22q12 gene rearrangement, confirming a positive result for EWSR1 gene rearrangement.[8]

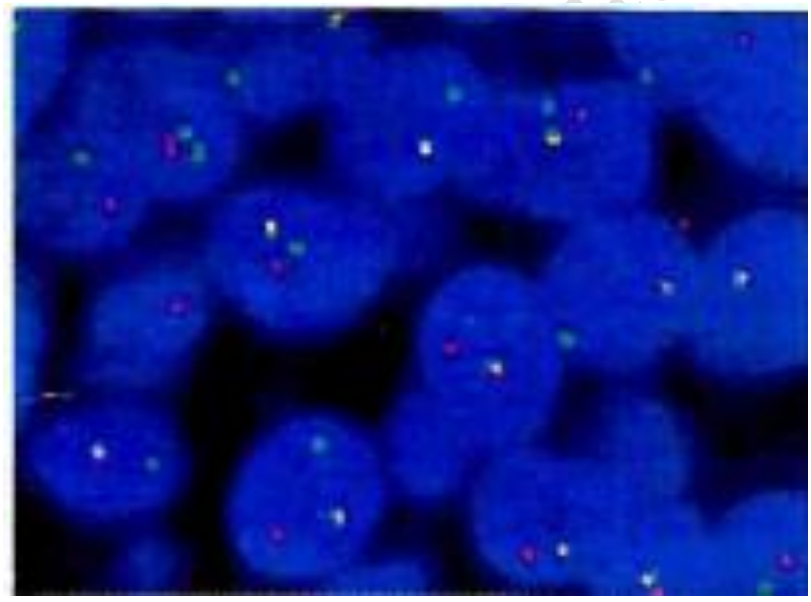

**Fig. 9**. fluorescence in situ hybridization analysis showed EWSR1 (22q12) gene rearrangement

The final diagnosis was obtained in association with molecular studies of the anterior abdominal wall mass strongly suggest the presence of the Ewing sarcoma family of tumors. This comprehensive analysis,

Eur J Clin Exp Med

encompassing histopathology, immunohistochemistry, and molecular studies, contributes to a nuanced understanding of the tumor's nature and aids in guiding further diagnostic and therapeutic considerations.

## Discussion

Extra skeletal Ewing's sarcoma is an exceedingly rare and aggressive soft tissue malignancy with distinct clinicopathological features.[9] Our case report highlights a 57-year-old female presenting with a left iliac fossa mass, ultimately diagnosed as extra skeletal Ewing sarcoma through a comprehensive diagnostic approach. The rarity of this condition in an older age group underscores the importance of recognizing atypical presentations and conducting thorough investigations. Microscopically, the tumor exhibited sheets of malignant small round cells with hyperchromatic nuclei, indistinct nucleoli, and occasional mitosis. The IHC panel, including markers like vimentin, CD99, synaptophysin, and FLI-1, provided crucial insights into the tumor's characteristics, confirming its affiliation with the Ewing sarcoma family of tumors. The positive result for EWSR1 gene rearrangement via fluorescence in situ hybridization further supported the diagnosis.

The clinical presentation of extra-skeletal Ewing sarcoma is often nonspecific, contributing to diagnostic challenges. In our case, the mass was initially identified due to severe abdominal pain, emphasizing the importance of considering extra-skeletal Ewing sarcoma in the differential diagnosis of abdominal masses, even in older individuals. The management of extra-skeletal Ewing sarcoma involves a multidisciplinary approach, integrating surgery, chemotherapy, and sometimes radiation therapy. Prognosis remains guarded, with a high recurrence rate and metastatic potential, particularly to the lungs and bones. The tenacious nature of this tumor necessitates close follow-up and vigilant monitoring to detect recurrence or metastasis promptly.[7,10]

This case report contributes to the existing literature by shedding light on an atypical presentation of extra-skeletal Ewing sarcoma in an older patient. Understanding the varied clinical manifestations and incorporating advanced diagnostic techniques, such as fluorescence in situ hybridization and IHC, is pivotal for accurate diagnosis and optimal patient management.

ONLINE FIRST Eur J Clin Exp Med

## Declarations

### *Funding*

No funding agencies are involved. Self-funded by the authors.

### *Author contributions*

Conceptualization, K.N.; Methodology, K.N., N.P.R., S.L.N. and A.S.; Software, K.N. and M.P.B.; Validation, K.N., M.P.B.; Formal Analysis, K.N.; Investigation, K.N., N.P.R., S.L.N. and A.S.; Resources, K.N.; Data Curation, K.N.; Writing – Original Draft Preparation, K.N. and M.P.B.; Writing – Review &

Editing, K.N. and M.P.B.; Visualization, K.N.; Supervision, K.N., N.P.R., S.L.N. and A.S.; Project Administration, K.N.; Funding Acquisition, K.N., N.P.R., S.L.N., A.S. and M.P.B.

***Conflicts of interest***

All authors declare that they have no conflicts of interest.

***Data availability***

Data available on request due to privacy/ethical restrictions.

***Ethics approval***

Approved by Bharat Heavy Electricals Limited, Power Sector Southern Region, Chennai, Tamilnadu, India.

**References**


1. Wang CC, Schulz MD. Ewing's sarcoma: a study of fifty cases treated at the Massachusetts General Hospital, 1930-1952 inclusive. *N Engl J Med.* 1953;248(14):571-576. doi: 10.1056/NEJM195304022481401
2. Balamuth NJ, Womer RB. Ewing's sarcoma. *Lancet Oncol*. 2010;11(2):184-192. doi: 10.1016/S1470-2045(09)70286-4
3. Angervall L, Enzinger FM. Extraskeletal neoplasm resembling Ewing's sarcoma. *Cancer*. 1975;36(1):240-251. doi: 10.1002/1097-0142(197507)36:1<240::aid-cncr2820360127>3.0.co;2-h
4. Applebaum MA, Worch J, Matthay KK, et al. Clinical features and outcomes in patients with extraskeletal Ewing sarcoma. *Cancer*. 2011;117(13):3027-3032. doi: 10.1002/cncr.25840
5. Juurikka K, Butler GS, Salo T, Nyberg P, Åström P. The Role of MMP8 in Cancer: A Systematic Review. *Int J Mol Sci*. 2019;20(18):4506. doi: 10.3390/ijms20184506.
6. Pankratjevaite L, Eskandarani HA, Lizdenis P, Saladzinskas Z. Challenges in diagnosing an extraosseous Ewing sarcoma: A case report. *Int J Surg Case Rep*. 2022;91(106708):106708. doi: 10.1016/j.ijscr.2021.106708
7. Gaspar N, Hawkins DS, Dirksen U, et al. Ewing sarcoma: Current management and future approaches through collaboration. *J Clin Oncol*. 2015;33(27):3036-3046. doi: 10.1200/JCO.2014.59.5256
8. Mcgowan-Jordan J, Hastings R, Moore J. *ISCN2020:An International System for Human Cytogenomic Nomeclature (2020)(Cytogenetic and Genome Research )*. 2020.
9. Chai J, Hyuk MD, Phd, Ro JY. PhD The 2020 WHO Classification of Tumours of soft tissue: selected changes and new entities. *Adv Anat Pathol.* 2021;28(1):44-58. doi: 10.1097/PAP.0000000000000284
10. Thacker MM, Humble S, Zhang C, Gokaslan ZL, Galindo RL, Wadhwa R. Surgical outcomes for Ewing sarcoma of the spine: A systematic review. *Spine*. 2010;35:1400-1410.


ONLINE FIRST Eur J Clin Exp Med